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Radiation-induced alterations in prostaglandin excretion in the rat

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RADIATION-INDUCED ALTERATIONS IN PROSTAGLANDIN EXCRETION IN THE RAT

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Summary

Dose-related alterations in the levels of prostaglandins ($PGF_{2\alpha}$ and PGE) and thromboxane B_2 (TxB_2) were observed in the urine of unanesthetized rats following whole-body gamma radiation. Exposure doses of 100 and 900 rads resulted in significant changes in urinary levels of these cyclooxygenase products. These findings suggest the potential use of radioimmunoassay measurement of urinary prostaglandins and thromboxane as a noninvasive indicator of radiation exposure.

Exposure to ionizing radiation induces subcellular biochemical and molecular alterations, which may result in cellular destruction. The biochemical changes that occur are often reflected as alterations in the composition of physiological fluids, which may be useful indicators not only of radiation injury but also of the extent of radiation exposure. The kidney is an important route for the elimination of endogenously derived biochemicals, and the analysis of substances in the urine of irradiated animals provides a noninvasive means for estimating radiation damage *in vivo*.

A number of reports exist on the increased concentrations of various metabolites in the urine following whole-body irradiation. Several of these show a reasonably linear correlation with radiation dose within limited dose ranges. Pařízek *et al.* (1) found increases in deoxycytidine (CdR) excretion in rat urine in the first 24 hrs after whole-body irradiation (50-600 R). The biochemical origin of the excreted CdR (a degradation product derived from polydeoxyribonucleotide metabolism) was shown to be considerably reduced in splenectomized rats, suggesting early radiation-induced cellular destruction as the source of this urinary metabolite (2). Investigations of creatinine excretion revealed that during the initial 4 days after exposure to 25-650 rads of x-rays, the averaged creatinine excretion varied linearly with the dose received (3). A linear relationship between the daily excretion of taurine and urea was observed following whole-body exposure of rats to 75-250

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rads of x-rays (4). However, this radiation-induced secretion of taurine was shown to be species dependent (5). The source of the radiation-induced increase in taurine excretion was shown to be the pancreas, with possible contributions from the liver and intestines. Spleen, adrenals, hypophysis, and kidneys were shown not to be involved in this phenomenon (6).

Elevations in prostaglandin (PG) levels following irradiation have been reported in lung parenchymal and airway tissues (7,8), liver and spleen (9,10), skin (11), and the small intestine (12) in a variety of laboratory animals. The present study was undertaken to determine whether PG and TxB_2 levels in the urine may reflect these alterations in metabolism in animals exposed to whole-body gamma radiation from a cobalt-60 source. In order to assess the use of this measurement as a biological indicator of radiation damage, we investigated the urinary excretion rates of these substances in rats at various time intervals pre- and postexposure to 100 and 900 rads.

Materials and Methods

Materials

Rabbit $PGF_{2\alpha}$ and PGE_2 antisera were obtained from Clinical Assays (Cambridge, MA) and Accurate Chemical and Scientific Co. (Hicksville, NY), respectively. $PGF_{2\alpha}$, PGE_2 and TxB_2 were the generous gifts of Dr. John Pike (Upjohn Co., Kalamazoo, MI). [^{3}H]-$PGF_{2\alpha}$ (120 Ci/mmol), [^{3}H]-PGE_2 (140 Ci/mmol), and [^{3}H]-TxB_2 (125 Ci/mmol) were purchased from New England Nuclear (Boston, MA). TxB_2 antisera were prepared in rabbits; an IgG-rich fraction was produced by affinity chromatography on a protein A-Sepharose CL-4B column (Pharmacia, Uppsala, Sweden). Trizma and gelatin (Bloom-100) were products of Sigma Chemical Co. (St. Louis, MO). Norit-A was purchased from Fisher Scientific Co. (Pittsburgh, PA), and Dextran T-70 obtained from Pharmacia.

The specificity of the antisera employed was characterized, and the ratio of PG concentration to the cross-reacting substance concentration at 50% inhibition of maximum binding was determined. TxB_2 antiserum demonstrated less than 2% cross-reactivity with other arachidonic acid metabolites ($PGF_{2\alpha}$, PGE_2, PGD_2 and 6-keto $PGF_{1\alpha}$). Specificity of the commercially prepared antiserum to $PGF_{2\alpha}$ demonstrated only minor cross-reactivity with 6-keto $PGF_{1\alpha}$ (<12%), whereas anti-PGE_2 did not distinguish between PGE_1 and PGE_2 (0.1-2.0% cross-reactivity with $PGF_{2\alpha}$, PGD_2, 6-keto $PGF_{1\alpha}$ and TxB_2). Therefore, the data are expressed as PGE to indicate this cross-reactivity of anti-PGE_2 with PGE_1.

Animal Experiments and Irradiation

Male Sprague-Dawley rats (Taconic Farms, Inc., Germantown, NY) weighing 200-300 g were housed in individual metabolic cages, fed a bolus of food daily, and allowed water *ad libitum*. The animals were maintained in the cages for 7 days before any urine collections were made to allow them to acclimate to the new environment. Three days prior to irradiation, urine was collected at 24-hour intervals and its volume was measured. Postirradiation collections were made and urine volume measured at the end of the following time intervals: 0-1, 1-3, 3-6, 6-12, 12-24, 24-48, 48-72, and 72-96 hours. The urines were collected in 5 to 50 µl of 10 N HCl, depending on the urine volume. Immediately after collection, 475 µl aliquots of urine were added to 25 µl perchloric acid (PCA) (final concentration 0.04 N PCA); they were mixed and stored at -80° C for later analysis. Preliminary analyses revealed no significant differences in the levels of PG or thromboxane measured in the supernatants of PCA-precipitated urines compared to non-PCA-precipitated urines. However, even the latter urine samples stored frozen until analysis, required centrifugation to remove particulate material prior to radioimmunoassay. On the day of analysis, all

samples were thawed at room temperature and centrifuged (13,000 x g) at 4° C for 15 min to remove PCA-precipitated protein; supernatants were then assayed for PG level.

Animals were placed in individual lucite boxes and irradiated in groups of ten, with 100 or 900 rads of gamma radiation from a Theratron 80 ^{60}Co source (1.17 and 1.33 MeV gamma). The dose rate was 40.2-41.0 rad/min with a target distance of 112-115 cm and a tissue/air ratio of 0.89. A wax rat phantom with an ion chamber placed at midline was used to determine absorbed dose. Post-irradiation survival of animals subjected to 900 rads at this dose rate ranged from 7 to 14 days.

Prostaglandin Analysis

PG analysis was performed by a modification (13) of the radioimmunoassay technique of Jaffe et al. (14). The assay consists of incubating 20-100 µl of the PCA-precipitated urine-derived supernatant or known standards (2.5-1000 picograms PG) with antisera (50 µl) for 2 hours at 22° C. When less than 100 µl of the sample was used, the volume was brought to 100 µl by the addition of Trizma buffer (Trizma 0.012%, NaCl 0.083%, gelatin 0.1%, pH 7.4). Thereafter, 50 µl $^{3}[H]$-PG (8000 CPM) was added and the incubation continued at 4° C for 12 to 16 hours (final volume 200 µl). The bound $^{3}[H]$-PG was separated from the uncomplexed tracer after the addition of 250 µl ice cold Trizma-NaCl-gelatin (1.0%) by adding 500 µl cold charcoal (0.5%)-dextran (0.05%) in Trizma-NaCl and incubating at 4° C for 20 min following centrifugation (200 x g for 12 min at 4° C). The supernatant was then decanted into scintillation vials. Ten ml ultrafluor was added, and the radioactivity was determined by scintillation spectrometry. All radioimmunoassays were performed in duplicate.

Data and Statistical Analysis

Experimental data for each animal at each collection time was recorded as urinary PG concentration in pg/ml and urinary excretion rate in ml/hr and then converted to pg/hr. These values were determined for all intervals (pre- and postirradiation). Thus each value reflects a rate of PG accumulation occurring since the previous collection interval. For each animal, the three 24-hour preirradiation values were averaged, and this average served as a baseline control value for that animal. All pre- and postirradiation values were expressed as a fraction (percent) of their preirradiation control level for each animal. In this way, employing each animal as its own control reduced animal-to-animal variation. A log transformation of these data was then made and a student's t test for unpaired samples was applied to determine significance (15) between postirradiation values of urinary PG and control value (100 percent). The data are presented as the geometric means (n=10) expressed as the percent of mean control values (pg/hr), calculated as described. Error bars in Figure 1 and the tabulated errors in Table I express the antilogged mean plus and minus one standard error of the mean (S.E.M.). The preirradiation 24-hour values for individual animals in pg/ml varied from 39.0 to 3719.1 (pg/ml PGE), 10.0 to 125.2 (pg/ml $PGF_{2\alpha}$), and 63.0 to 2472.5 (pg/ml TxB_2).

Results

Alterations in PG and TxB_2 (pg/hr) excretion patterns following a low (100 rads) and high (900 rads) dose of whole-body gamma radiation are presented on the following figures. Significant differences from preirradiation values for urinary levels of PGE (Fig. 1) were found at 12, 24, and 96 hrs postexposure to 100 rads. No significant difference occurred at 3 and 6 hrs postirradiation. In a separate experiment (data not shown), rats subjected to 300

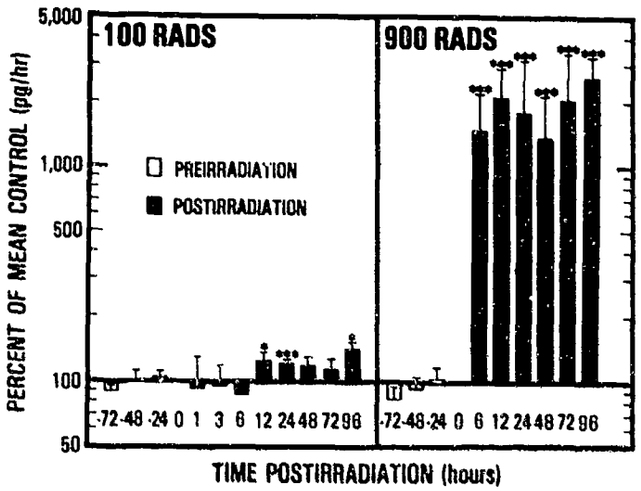

FIG. 1

Urinary levels of PGE following gamma irradiation. Values represent the geometric means (n=10) in pre-and postirradiated urine samples (see text). Error bars express the antilogged mean plus one S.E.M. * = (0.05≥p>0.01); *** = (0.001≥p).

rads (n=4) demonstrated significant increases at 3, 6, and 12 hrs postirradiation. Levels returned to preirradiation values at 24 hrs and remained at these levels for the duration of the study (96 hrs). These data suggest a significant and transient increase in PGE levels at an intermediate dose level. Exposure to 900 rads resulted in highly significant ($p \geq 0.001$) elevations in urinary PGE excretion, detected at 6-96 hrs postirradiation.

Urinary TxB_2 concentrations are shown in Fig. 2. Significant increases in the TxB_2 excretion rate are seen at 1, 3, and 6 hrs after receiving 100 rads of gamma radiation. This is followed by a decline to control values (12 hr) and intermittent decreases significantly below those of controls at 36, 60, and 84 hrs. Analysis of urinary TxB_2 concentrations from animals receiving 900 rads revealed dramatic elevations in TxB_2 excretion, without recovery, throughout the duration of these experiments.

The effects of gamma radiation on urinary $PGF_{2\alpha}$ levels are shown in Fig. 3. At 100 and 900 rads, postirradiation $PGF_{2\alpha}$ levels were significantly elevated above control levels at 12 hrs. Animals receiving 100 rads demonstrated a significant reduction in $PGF_{2\alpha}$ excretion at 60 hrs. Following 900 rads of gamma radiation, a second statistically significant peak of elevated $PGF_{2\alpha}$ excretion was found to occur at 36 hrs. All other postirradiation values were not significantly different from control values.

The values for PGE, $PGF_{2\alpha}$, and TxB_2 excretion rates for sham-irradiated animals (n=5) are presented in Table I. The values indicate minimal variation from the pre-sham-irradiated (control) levels. Significant decreases in excretion rates were observed at 6 hrs (PGE) and at 6 and 48 hrs ($PGF_{2\alpha}$). However, these changes are in the opposite direction to the significant increases observed following radiation. At all other time intervals, urinary levels of PGE, $PGF_{2\alpha}$

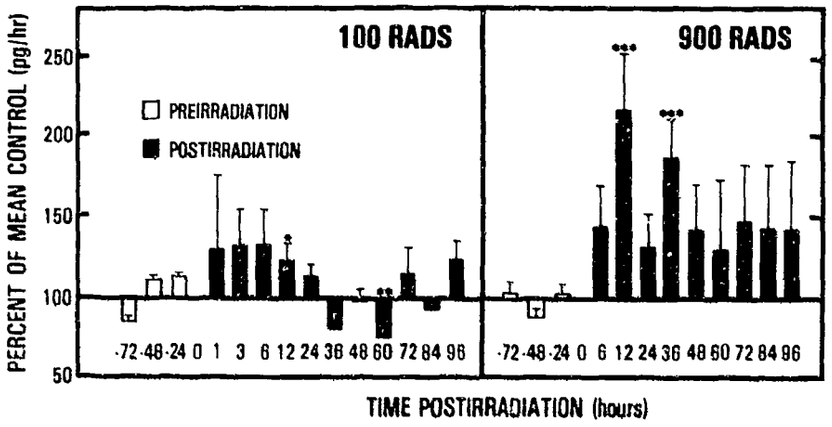

FIG. 2

Urinary levels of thromboxane B_2 following gamma irradiation. Values represent the geometric means (n=10) in pre- and postirradiated urine samples (see text). Error bars express the antilogged mean plus one S.E.M. * = (0.05≥p>0.01); ** = (0.01≥p>0.001); *** = (0.001≥p).

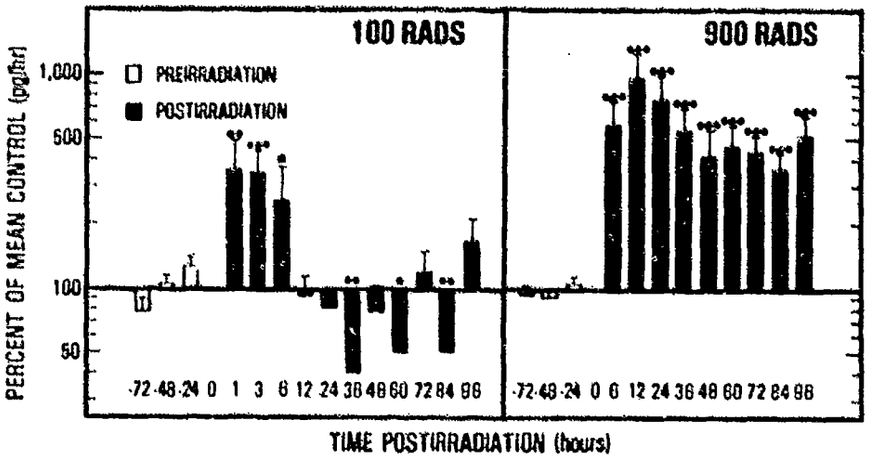

FIG. 3

Urinary levels of $PGF_{2\alpha}$ following gamma irradiation. Values represent the geometric means (n=10) in pre- and postirradiated urine samples (see text). Error bars express the antilogged mean plus one S.E.M. * = (0.05≥p>0.01); ** = (0.01≥p>0.001); *** = (0.001≥p).

TABLE I

Prostaglandin Content in Urine of Sham-Irradiated Rats

Time (hrs) Sham Irradiation	-72	-48	-24	3	6	12	24	48	72	96
Prostaglandin % of Control (pg/hr)*										
PGE	74.5 +11.29 - 9.81	104.4 + 5.20 - 4.96	115.7 +10.75 - 9.83	127.3 +32.75 -26.05	44.8# +10.32 - 8.39	44.2 +15.22 -11.32	92.1 +21.10 -17.16	60.3 +17.89 -13.80	83.5 +14.62 -12.44	86.4 +24.44 -19.05
TxB_2	83.1 + 7.50 - 6.87	96.5 + 6.05 - 5.69	117.0 + 9.43 - 8.73	147.0 +76.12 -50.15	70.5 +13.84 -11.56	67.5 + 8.91 - 7.88	98.6 + 8.74 - 8.03	85.6 +12.03 -10.54	104.7 +19.86 -16.70	90.6 +13.27 -11.57
$PGF_{2\alpha}$	78.5 + 2.98 - 2.87	101.5 + 3.89 - 3.75	119.3 + 2.85 - 2.78	112.8 +15.22 -13.40	56.6## + 5.42 - 4.94	84.5 +14.81 -12.61	84.9 + 5.70 - 5.33	72.6# + 8.22 - 7.38	92.1 + 8.21 - 7.55	99.6 + 8.14 - 7.52

* (See text for method of computation) shown as geometric mean ± SEM

Urinary PGE, TxB_2, and $PGF_{2\alpha}$ levels in sham-irradiated rats. The underlined values represent excretion rates presented as geometric means, $\bar{X}$, (n=5) expressed as percent of preirradiated control values (see text). Values listed below the geometric mean indicate plus one S.E.M.[1] and minus one S.E.M.[2]. # = $(0.05 \geq p > 0.01)$; ## = $(0.01 \geq p > 0.001)$.

[1] $=[10^{(\bar{X} + S.E.M.)} - \bar{X}]$; [2] $=[\bar{X} - 10^{(\bar{X} - S.E.M.)}]$

and TxB_2 did not differ significantly from controls.

In summary, urinary PGE, $PGF_{2\alpha}$, and TxB_2 levels demonstrate dose-related increases in excretion rates following whole-body gamma irradiation. Both total mean increases and temporal relationships of these increases differ depending on the type of PG investigated. The order of the magnitude of the increases in urinary excretion rates following 900 rads was PGE > TxB_2 > $PGF_{2\alpha}$.

Discussion

Distinct increases in PG and TXB_2 excretion as determined by radioimmunoassay of these substances in rat urine (16,17) have been demonstrated following whole-body gamma irradiation. Several explanations are possible for the marked increases in urinary PGE and TXB_2 levels (900 rads) without recovery (Figs. 1 and 2). These may include (a) radiation-induced alterations in prostaglandin metabolism resulting in increased tissue and circulatory levels, (b) radiation effects on the kidney resulting in increased excretion of PG and blood proteins which bind PG, and/or (c) direct cellular destruction and subsequent release of PG.

The patterns of prostaglandin excretion observed following whole-body gamma radiation demonstrate increases in excretion rates in addition to temporal changes in these increases that vary with the type of PG determined. Several studies indicate alterations in enzyme activity may be responsible for the increased synthesis of PGE and $PGF_{2\alpha}$ (18) and TxB_2 (19,20). In the irradiated animal, $PGF_{2\alpha}$, PGE, and TxB_2 were found to be significantly elevated in parenchymal lung tissues (7). Furthermore, PGE and $PGF_{2\alpha}$ content increased in both rat (9) and mouse (10) liver and spleen tissues at 3-6 hours after 1000 rads gamma radiation. Skin PG levels were also found to increase following ultraviolet irradiation (11). Postirradiation increases in small intestinal motility in mice (600 rads) have been correlated with an increase in PGE activity, and they were demonstrated to be inhibited by the cyclooxygenase inhibitor indomethacin (12). Eisen and Walker (21) have reported a decrease in prostaglandin 15-OH dehydrogenase following radiation in the small intestine of the mouse, whereas lung tissue demonstrated significant increases in this enzyme (22). These findings suggest that in the irradiated animal, prostaglandin levels in a variety of tissues are markedly altered and normal clearance mechanisms may not be effective. Therefore, the increases in urinary PG levels following whole-body irradiation observed in this study may reflect alterations in PG anabolism/catabolism.

Since urinary PG levels in the nonirradiated animal are an indication of kidney physiology and pathology (23), the observed increases may be partly attributed to the effects of radiation on kidney physiology. To what extent these increased PG excretion values reflect renal prostaglandin release and/or synthesis, compared to the contributions by other tissue and cellular types, could not be determined in the present experiments. It is well established that PG's bind to serum proteins, notably albumin, in the rat (24), and the quantity of PG bound to this secreted albumin may reflect PG release from a number of tissues within the body following high doses of radiation (25). Alterations in protein excretion have been observed in rats following whole-body irradiation (900 rads) (26). Urinary protein determinations revealed significant increases at 2, 3, 6, 9, 12, and 24 hrs. During 24 hours, sham-irradiated animals excreted 2.04 ± 0.169 mg protein while irradiated animals excreted 4.05 ± 0.143 mg. In the present study, all urine samples were stored frozen (-80° C) and analyzed at the same time. Precipitated material was apparent in non-PCA treated, HCl-acidified urine samples, and was removed

before analysis as indicated in Methods. We found no significant differences in PG concentrations in samples with or without PCA precipitation.

Cellular destruction resulting from whole-body irradiation may also contribute to enhanced PG release and subsequent increased urinary levels. The observed increases in urinary PG and TxB_2 following radiation may result from a partial contribution of each of the above stated possible mechanisms.

While the origin of increased urinary PG has not been elucidated, the significant dose-related, radiation-induced increases in PGE and TxB_2 excretion suggest a potential use for these substances as biological indicators of radiation damage. Effective biological dosimetry may require a full spectrum of chemical analyses in the urine as well as of plasma and cellular elements in the blood in order to obtain a reasonable estimation of radiation dose following whole-body radiation. This study suggests that PGE and TxB_2 as well as other metabolites of arachidonic acid metabolism found in the urine may be of value in determining the extent of radiation injury. Further studies are currently in progress to determine the effects of radiation on kidney PG metabolism as well as circulatory PG levels, in an effort to delineate the origin(s) of the observed alterations in urinary PG and TxB_2 excretion.

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